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=> s human (a) (liver or hepatocyte)
  12 FILES SEARCHED...
  23 FILES SEARCHED...
  39 FILES SEARCHED...
  52 FILES SEARCHED...
  68 FILES SEARCHED...
L1      122169 HUMAN (A) (LIVER OR HEPATOCYTE)

=> s hepg2
  34 FILES SEARCHED...
  82 FILES SEARCHED...
L2       49624 HEPG2

=> s l1 or l2
  33 FILES SEARCHED...
  90 FILES SEARCHED...
L3      166808 L1 OR L2

=> s (p450 or cyp) (3A) transfect
  40 FILES SEARCHED...
  88 FILES SEARCHED...
L4           0 (P450 OR CYP) (3A) TRANSFECT

=> s (450 or cyp) (3a) express
  40 FILES SEARCHED...
  76 FILES SEARCHED...
L5         613 (450 OR CYP) (3A) EXPRESS

=> s l5 and l3
  47 FILES SEARCHED...
L6          65 L5 AND L3

=> duplicate
ENTER REMOVE, IDENTIFY, ONLY, OR (?):remove
ENTER L# LIST OR (END):l6
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, BIOCOMMERCE, DGENE,
DRUGLAUNCH, DRUGMONOG2, DRUGUPDATES, FEDRIP, FOREGE, GENBANK, KOSMET,
MEDICONF, PHAR, PHARMAML, SYNTHLINE, CHEMLIST, HSDB, MSDS-CCOHS, MSDS-OHS,
RTECS, CONF, EVENTLINE, IMSDRUGCONF, DIOGENES, INVESTEXT, USAN, FORIS, FORKAT,
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L7           19 DUPLICATE REMOVE L6 (46 DUPLICATES REMOVED)

=> s l7 and (heterologous or transfect)
  15 FILES SEARCHED...
  40 FILES SEARCHED...
  63 FILES SEARCHED...
 75% OF LIMIT FOR L#S REACHED
L8           0 L7 AND (HETEROLOGOUS OR TRANSFECT)

=> d l7 1-19 bib ab

L7   ANSWER 1 OF 19  CAPLUS  COPYRIGHT 2002 ACS        DUPLICATE 1
AN   2002:248625  CAPLUS
DN   137:4273
TI   Cytochrome P450 2E1-derived reactive oxygen species mediate paracrine
```

stimulation of collagen I protein synthesis by hepatic stellate cells
AU Nieto, Natalia; Friedman, Scott L.; Cederbaum, Arthur I.
CS Department of Pharmacology and Biological Chemistry, Mount Sinai School of Medicine, New York, NY, 10029, USA
SO Journal of Biological Chemistry (2002), 277(12), 9853-9864
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB To evaluate possible fibrogenic effects of CYP2E1-dependent generation of reactive oxygen species, a model was developed using co-cultures of **HepG2** cells, which do (E47 cells) or do not (C34 cells) **express** cytochrome P **450** 2E1 (CYP2E1) with stellate cells. There was an increase in intra- and extracellular H2O2, lipid peroxidn., and collagen type I protein in stellate cells co-cultured with E47 cells compared with stellate cells alone or co-cultured with C34 cells. The increase in collagen was prevented by antioxidants and a CYP2E1 inhibitor. CYP3A4 did not mimic the stimulatory effects found with CYP2E1. Collagen mRNA levels remained unchanged, and pulse-chase anal. indicated similar half-lives of collagen I protein between both co-cultures. However, collagen protein synthesis was increased in E47 co-culture. Hepatocytes from pyrazole-treated rats (with high levels of CYP2E1) induced collagen protein in primary stellate cells, and antioxidants and CYP2E1 inhibitors blocked this effect. These results suggest that increased translation of collagen mRNA by CYP2E1-derived reactive oxygen species is responsible for the increase in collagen protein produced by the E47 co-culture. These co-culture models may be useful for understanding the impact of CYP2E1-derived ROS on stellate cell function and activation.
RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AN 2002:236730 BIOSIS
DN PREV200200236730
TI Cyclosporin A-induced free radical generation is not mediated by cytochrome P-450.
AU Krauskopf, Alexandra; Buetler, Timo M.; Nguyen, Nathalie S. D.; Mace, Katherine; Ruegg, Urs T. (1)
CS (1) Pharmacology Group, School of Pharmacy, University of Lausanne, 1015, Lausanne: Urs.Ruegg@dpharm.unil.ch Switzerland
SO British Journal of Pharmacology, (February, 2002) Vol. 135, No. 4, pp. 977-986. print.
ISSN: 0007-1188.
DT Article
LA English
AB 1 Reactive oxygen species (ROS) have been proposed to play a role in the side effects of the immunosuppressive drug cyclosporin A (CsA). 2 The aim of this study was to investigate whether cytochrome P-450 (CYP) dependent metabolism of CsA could be responsible for ROS generation since it has been suggested that CsA may influence the CYP system to produce ROS. 3 We show that CsA (1-10 muM) generated antioxidant-inhibitable ROS in rat aortic smooth muscle cells (RASMC) using the fluorescent probe 2,7-dichlorofluorescin diacetate. 4 Using cytochrome c as substrate, we show that CsA (10 muM) did not inhibit NADPH cytochrome P-450 reductase in microsomes prepared from rat liver, kidney or RASMC. 5 CsA (10 muM) did not uncouple the electron flow from NADPH via NADPH cytochrome P-450 reductase to the CYP enzymes because CsA did not inhibit the metabolism of substrates selective for several CYP enzymes that do not metabolize CsA in rat liver microsomes. 6 CsA (10 muM) did not generate more radicals in CYP 3A4 expressing immortalized **human liver** epithelial cells (T5-3A4 cells) than in control cells that do not **express** **CYP** 3A4. 7 Neither diphenylene iodonium nor the CYP 3A inhibitor

ketoconazole were able to block ROS formation in rat aortic smooth muscle or T5-3A4 cells. 8 These results demonstrate that CYP enzymes do not contribute to CsA-induced ROS formation and that CsA neither inhibits NADPH cytochrome P-450 reductase nor the electron transfer to the CYP enzymes.

L7 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
AN 2002:733727 CAPLUS
TI Bioreductively activated antitumor N-oxides: the case of AO4N, a unique approach to hypoxia-activated cancer chemotherapy
AU Patterson, Laurence H.
CS Department of Pharmaceutical and Biological Chemistry, School of Pharmacy, University of London, London, WC1N 1AX, UK
SO Drug Metabolism Reviews (2002), 34(3), 581-592
CODEN: DMTRAR; ISSN: 0360-2532
PB Marcel Dekker, Inc.
DT Journal
LA English
AB Aliph. amine N-oxides have long been identified as non-toxic metabolites of a large no. of tertiary amines drugs. Bioredn. of such N-oxides will generate the active parent amine. This principle has been adopted to develop AQ4N, a di-N-oxide anticancer prodrug with little intrinsic cytotoxicity. However, AQ4N is bioreduced in hypoxic regions of solid tumors and micrometastatic deposits to generate a cytotoxic alkylaminoanthraquinone metabolite. The 4-electron redn. metabolite of AQ4N has high affinity for DNA and is a potent inhibitor of topoisomerase II, a DNA processing enzyme crucial to cell division. The development of AQ4N has proceeded on many fronts in order to establish this unique anticancer prodrug opportunity. Preclin. studies in vivo have demonstrated that although AQ4N has little or no intrinsic cytotoxic activity per se it (i) enhances the antitumor effects of radiation and conventional chemotherapeutic agents, (ii) is pharmaco-kinetically stable, and (iii) is a substrate for cytochrome P 450 (CYP). A study of AQ4N metab. in vitro and ex vivo using purified CYP enzymes, phenotyped **human livers** and CYP transfected cell lines shows that CYP3A, 1A and 1B1 family members contribute to AQ4N bioredn. in the absence of oxygen. Importantly AQ4N is shown to be metabolized by tumors known to **express CYP** isoforms. AQ4N is currently in Phase I clin. trials.
RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
AN 2002:130703 BIOSIS
DN PREV200200130703
TI Comparative aflatoxin B1 activation and cytotoxicity in human bronchial cells expressing cytochromes P450 1A2 and 3A4.
AU Van Vleet, Terry R.; Mace, Katherine; Coulombe, Roger A., Jr. (1)
CS (1) Graduate Toxicology Program, Utah State University, 4620 Old Main Hill, Logan, UT, 84322-4620: rogerc@cc.usu.edu USA
SO Cancer Research, (January 1, 2002) Vol. 62, No. 1, pp. 105-112.
http://cancerres.aacrjournals.org/. print.
ISSN: 0008-5472.
DT Article
LA English
AB Some epidemiological evidence suggests a link between the inhalation of aflatoxin B1 (AFB1)-contaminated grain dusts and increased lung cancer risk. However, the mechanisms of AFB1 activation and action in human lung are not well understood. We compared AFB1 action in SV40 immortalized human bronchial epithelial cells (BEAS-2B) with two transfected cell lines that stably **express** human cytochromes P450 (**CYPs**) 1A2 (B-CMV1A2) and 3A4 (B3A4), the principal CYPs thought to activate this mycotoxin in **human liver**. All three cell types

retained catalytically active glutathione S-transferase, the key phase II enzyme that detoxifies metabolically activated AFB1. B-CMV1A2 and B3A4 cells expressed methoxy-resorufin-O-demethylase (MROD) and nifedipine oxidase activities, respectively, and were 3000-and 70-fold more susceptible, respectively, to the cytotoxic effects of AFB1 than the control cell line (BEAS-2B). When cultured with a range of low, environmentally relevant AFB1 concentrations (0.02-1.5 muM), control cells formed barely detectable AFB1-DNA adducts, whereas B-CMV1A2 cells formed significantly more adducts than B3A4 cells. In B-CMV1A2 cells, formation of AFB1-DNA adducts was inhibited by the CYP 1A2 inhibitor 7,8-benzoflavone, whereas formation of AFB1-DNA adducts in B3A4 cells was inhibited by the CYP 3A4 inhibitor 17alpha-ethynylestradiol. Competitive reverse transcription-PCR analysis showed that only the CYP-transfected cell lines expressed CYP mRNA. When adjusted for CYP mRNA expression, B-CMV1A2 cells were more efficient in the formation of cytotoxic and DNA-alkylating species at low AFB1 concentrations, whereas B3A4 cells were more efficient at high concentrations. Our results affirm the hypothesis that, as in **human liver** microsomes, CYP 1A2 in human lung cells appears to have a more important role than CYP 3A4 in the bioactivation of low AFB1 concentrations associated with many human exposures. Therefore, it is possible that under conditions in which appropriate CYPs are expressed in lung, inhalation of AFB1 may result in increased risk of lung cancer in exposed persons.

L7 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 5
AN 2000:352541 CAPLUS
DN 133:87301
TI CYP2E1 overexpression in **HepG2** cells induces glutathione synthesis by transcriptional activation of .gamma.-glutamylcysteine synthetase
AU Mari, Montserrat; Cederbaum, Arthur I.
CS Department of Biochemistry and Molecular Biology, Mount Sinai School of Medicine, New York, NY, 10029, USA
SO Journal of Biological Chemistry (2000), 275(20), 15563-15571
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Induction of CYP2E1 (cytochrome P 450 2E1) by ethanol appears to be one of the central pathways by which ethanol generates a state of oxidative stress. CYP2E1 is a loosely coupled enzyme; formation of reactive oxygen species occurs even in the absence of added substrate. GSH is crit. for preserving the proper cellular redox balance and for its role as a cellular protectant. Since cells must maintain optimal GSH levels to cope with a variety of stresses, the goal of this study was to characterize the GSH homeostasis in human hepatocarcinoma cells (**HepG2**) that overexpress CYP2E1. This study was prompted by the finding that toxicity in CYP2E1-overexpressing cells was markedly enhanced after GSH depletion by buthionine sulfoximine treatment. CYP2E1-overexpressing cells showed a 40-50% increase in intracellular H2O2; a 30% increase in total GSH levels; a 50% increase in the GSH synthesis rate; and a 2-fold increase in .gamma.-glutamylcysteine synthetase heavy subunit (GCS-HS) mRNA, the rate-limiting enzyme in GSH synthesis. This GCS-HS mRNA increase was due to increased synthesis since nuclear run-on assays showed increased transcription in CYP2E1-expressing cells, and the GCS-HS mRNA decay after actinomycin D treatment was similar in CYP2E1-expressing cells and empty vector-transfected cells. The facts that treatment with GSH Et ester almost completely prevented the increase in GCS-HS mRNA and decreased H2O2 levels and that transient transfection with catalase (but not manganese-superoxide dismutase) produced a decrease in GCS-HS mRNA only in CYP2E1-expressing cells suggest a possible role for H2O2 in the induction of GCS-HS gene transcription. In contrast to results with **HepG2** cells expressing CYP2E1, no increase in GCS-HS mRNA was found with a **HepG2** cell line engineered to **express** human cytochrome P

**450** 3A4. In summary, CYP2E1 overexpression in **HepG2** cells up-regulates the levels of reduced GSH by transcriptional activation of GCS-HS; this may reflect an adaptive mechanism to remove CYP2E1-derived oxidants such as H2O2.

RE.CNT 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 19 USPATFULL
AN 1998:75376 USPATFULL
TI Screening method for the identification of compounds capable of abrogation HIV-1 gag-cyclophilin complex formation
IN Luban, Jeremy, New York, NY, United States
Goff, Stephen P., Tenafly, NJ, United States
PA The Trustees of Columbia University in the City of New York, New York, NY, United States (U.S. corporation)
PI US 5773225 19980630
AI US 1994-248357 19940524 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Budens, Robert D.; Assistant Examiner: Parkin, Jeffrey S.
LREP White, John P.
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN 15 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1351
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The human immunodeficiency virus type 1 (HIV-1) gag gene product is capable of directing the assembly of virion particles independent of other viral elements. The Gag protein also plays an important role during the early stages of viral replication. Employing the yeast two-hybrid system, a cDNA expression library was screened and two host proteins identified. These proteins, designated cyclophilins A and B (CyPsA and B), interacted specifically with the HIV-1 Gag polyprotein Pr55.sup.gag. Glutathione S-transferase-CyP fusion proteins bind tightly to Pr55.sup.gag in vitro. Cyclosporin A (CsA) efficiently disrupts the Gag-CyPA binding interaction. The identification of novel compounds capable of abrogating this protein-protein interaction employing the disclosed screening assay will facilitate the development of HIV-1 antiviral agents.

L7 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2002 ACS
AN 1999:8945 CAPLUS
DN 130:178657
TI Oxidative stress and cytotoxicity induced by ferric-nitrilotriacetate in **HepG2** cells that express cytochrome P450 2E1
AU Sakurai, Koichi; Cederbaum, Arthur I.
CS Department of Biochemistry, Mount Sinai School of Medicine, New York, NY, 10029, USA
SO Molecular Pharmacology (1998), 54(6), 1024-1035
CODEN: MOPMA3; ISSN: 0026-895X
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Iron can potentiate the toxicity of ethanol. Ethanol increases the content of cytochrome P 450 2E1 (CYP2E1), which generates reactive oxygen species, and transition metals such as iron are powerful catalysts of hydroxyl radical formation and lipid peroxidn. Expts. were carried out to attempt to link CYP2E1, iron, and oxidative stress as a potential mechanism by which iron increases ethanol toxicity. The addn. of ferric-nitrilotriacetate (Fe-NTA) to a **HepG2** cell line expressing CYP2E1 decreased cell viability, whereas little effect was obsd. in control cells not expressing CYP2E1. Toxicity in the CYP2E1-expressing cells was markedly enhanced after the depletion of

glutathione. Lipid peroxidn. was increased by Fe-NTA, esp. in cell exts. and medium from the CYP2E1-expressing cells. Toxicity was completely prevented by vitamin E or by 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, which also decreased the lipid peroxidn. Levels of ATP were lowered by Fe-NTA, and this was assocd. with a decreased rate of oxygen consumption by permeabilized cells with substrates donating electrons to complexes I, II, and IV of the respiratory chain. This mitochondrial damage was prevented by vitamin E. Toxicity was accompanied by DNA fragmentation, and this fragmentation was prevented by antioxidants. Overexpression of bcl-2 decreased the toxicity and DNA fragmentation produced by the combination of CYP2E1 plus Fe-NTA, as did a peptide inhibitor of caspase 3. These results suggest that elevated generation of reactive oxygen species in **HepG2** cells expressing CYP2E1 leads to lipid peroxidn. in the presence of iron, and the ensuing pro-oxidative state damages mitochondria, releasing factors that activate caspase 3, leading to a loss in cell viability and DNA fragmentation.

RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 6
AN 1997:165430 CAPLUS
DN 126:246704
TI Noninterference of cytochrome P4501A2 in the cytotoxicity of tacrine using genetically engineered V79 Chinese hamster cells for stable expression of the human or rat isoform and two **human hepatocyte** cell lines
AU Benoit, Guy G.; Naud, Carole F.; Simard, Marc A.; Astier, Alain L.
CS Toxicol. Lab., Henri Mondor Univ. Hosp., Creteil, 94010, Fr.
SO Biochemical Pharmacology (1997), 53(3), 423-427
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier
DT Journal
LA English
AB Tacrine (THA) is the only drug currently approved for the treatment of Alzheimer's disease. A common side effect of this drug in humans is major hepatotoxicity. THA-induced toxicity may be related to a metabolic pathway implicating cytochrome P 450 1A2 (CYP1A2). The purpose of this study was to clarify the role of the metabolic conversion of THA by CYP1A2 in the cytotoxicity of THA. The cytotoxicity of THA was evaluated in two **human hepatocyte** cell lines, **HepG2** and Chang liver, and on the V79 Chinese hamster cell line, which does not **express** cytochrome P **450** activity, and its variants, genetically engineered for expression of human or rat CYP1A2. Cells expressing human CYP1A2 metabolized THA to form its 1-OH deriv. (Vmax = 9.36 pmol min-1 mg-1 total protein), whereas no metab. was obsd. with the nonexpressing parental cells. In all cell lines, THA induced a marked decrease in cell viability and a strong inhibition of RNA and protein synthesis. However, these cytotoxic effects did not differ in parental V79 cells and variant cells expressing human or rat CYP1A2. The IC50 were tenfold higher for cell viability than for RNA and protein inhibition after 3 h of incubation but were similar after 24 h, indicating that this early inhibition was not a transient effect and could lead to cell death. These results strongly suggest that THA-induced cytotoxicity is not mediated by CYP1A2.

L7 ANSWER 9 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 7
AN 1997:259246 BIOSIS
DN PREV199799558449
TI Glycerol increases content and activity of human cytochrome P-4502E1 in a transduced **HepG2** cell line by protein stabilization.
AU Yang, Ming-Xue; Cederbaum, Arthur J. (1)
CS (1) Biochemistry Dep., Box 1020, Mount Sinai Sch. Med., One Gustave L. Levy Place, New York, NY 10029 USA

SO Alcoholism Clinical and Experimental Research, (1997) Vol. 21, No. 2, pp. 340-347.
ISSN: 0145-6008.
DT Article
LA English
AB Glycerol is widely used to stabilize cytochrome P-450 and prevent its transformation to cytochrome P-420. The effect of glycerol on the content and activity of human cytochrome P-4502E1 (CYP2E1) in a **HepG2** cell line that stably and constitutively **expresses** this P-**450** was evaluated by immunoassays and oxidation of p-nitrophenol. Addition of 100 to 200 mM glycerol to the culture medium resulted in a 2 1/2- to 3-fold increase in the content and activity of CYP2E1 in microsomes isolated from the cells. Increases could be observed within 4 to 8 hr after addition of glycerol to the culture medium. Glycerol had no effect on the content of cytochrome b-5, or activities of NADPH-cytochrome P-450 reductase or NADH-cytochrome b-5, reductase. Upon the addition of cycloheximide to stop protein synthesis, CYP2E1 content and activity decreased with apparent half-lives of 6 and 4 hr, respectively. Glycerol prevented or decreased this loss of CYP2E1 content and activity. Labeling CYP2E1 with (35S)methionine, followed by pulse-chase experiments with cold methionine and immunoprecipitation of CYP2E1 indicated a half-life for CYP2E1 of apprx 3 hr. Glycerol increased the half-life to apprx 11 hr. Stabilization of CYP2E1 protein by glycerol was not additive or synergistic with the increase of CYP2E1 by ethanol or 4-methylpyrazole, suggesting that all three agents elevate CYP2E1 by a similar type of mechanism in this model. These results indicate that glycerol can interact with human CYP2E1 to stabilize it against proteolytic degradation, increasing the half-life of the enzyme and thereby elevating the content and activity of CYP2E1.

L7 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 8
AN 1998:409699 CAPLUS
DN 129:185134
TI Ethanol-related cytotoxicity catalyzed by CYP2E1-dependent generation of reactive oxygen intermediates in transduced Hep G2 cells
AU Chen, Qi; Cederbaum, Arthur I.
CS Department of Biochemistry, Mount Sinai School of Medicine, New York, NY, 10029, USA
SO Current Topics in Pharmacology (1997), 3, 67-76
CODEN: CTPCF5
PB Research Trends
DT Journal; General Review
LA English
AB A review with 77 refs. which describes the establishment of a human hepatoma Hep G2 subline which over-**expresses** human cytochrome P **450** 2E1 (CYP2E1). Hep G2 cells were chosen as the target because there is no detectable CYP2E1 expression in these cells, and because these cells contain active NADPH-cytochrome P 450 reductase and cytochrome b3. CYP2E1 expression in the transduced Hep G2 cells was shown by Western blot and Northern blot anal. with anti-human CYP2E1 1gG and a CYP2E1 cDNA probe, resp. The expressed CYP2E1 was catalytically active in oxidizing typical substrates, such as p-nitrophenol, aniline, dimethylnitrosamine, and ethanol, and in formation of reactive oxygen intermediates and catalysis of lipid peroxidn. Ethanol and acetaminophen were found to be cytotoxic to MV2E1-9 cells, which overexpress CYP2E1, and not to the control MV5 cells lacking detectable CYP2E1. Arachidonic acid, was also found to induce cytotoxicity and apoptosis in MV2E1-9 cells, but not in MV5 cells. GSH appears to be essential in protecting Hep G2 cells against CYP2E1-dependent cytotoxicity induced by these agents, since BSO treatment, which depletes cellular GSH, increased the cytotoxicity. The cytotoxicity and apoptosis found with EtOH and PUFA in the MV2E1-9 cells were prevented by several antioxidants, esp. vitamin E and the vitamin E analog, Trolox. Induction of a state of oxidative stress appears to play a central role in the CYP2E1-dependent cytotoxicity. The CYP2E1 content in

MV2E1-9 cells was stabilized by its substrates, including 4-methylpyrazole, pyrazole, ethanol, and glycerol. The increased CYP2E1 protein correlates with increased catalytic activity. The CYP2E1 degrdn. obsd. in Hep G2 cells is similar to that previously obsd. in rat and rabbit liver hepatocytes. Turnover is very rapid (half-life of 3 to 6 h) in the absence of stabilizing substrates or ligands. Some agents such as carbon tetrachloride inactivate CYP2E1 probably through binding, labilizing, and removing the heme from the enzyme. The MV2E1-9 cells appear to be a valuable model to study CYP2E1 regulation, CYP2E1-dependent formation of reactive oxygen intermediates, and CYP2E1-related cytotoxicity of ethanol, polyunsatd. fatty acid, and other hepatotoxins.

L7 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2002 ACS
AN 1996:550528 CAPLUS
DN 125:187466
TI Human umbilical vein endothelial cells express P450 2C8 mRNA: cloning of endothelial P450 epoxygenase
AU Lin, Jane H.-C.; Kobari, Yukage; Zhu, Yi; Stemerman, Michael B.; Pritchard, Kirkwood A. Jr.
CS Department of Experimental Pathology, New York Medical College, Valhalla, NY, 10595, USA
SO Endothelium (1996), 4(3), 219-229
CODEN: ENDTE9; ISSN: 1062-3329
PB Harwood
DT Journal
LA English
AB Human umbilical vein endothelial cells (EC) metabolize arachidonic acid (AA) through three major pathways--cyclooxygenase, lipoxygenase and cytochrome P 450 (P 450) isoenzymes. Previously, we have shown that pathophysiol. concns. of native low-d. lipoprotein (n-LDL) increase EC P 450-dependent epoxyeicosatrienoic acid (EET) prodn. The present study was designed to identify putative P 450 isoenzymes involved in EC epoxidn. of AA. Reverse transcription-polymerase chain reaction (RT-PCR) and rapid amplification of cDNA ends (RACE) were employed to detect P 450 2 family cDNA from EC mRNA. Degenerate primers complimenting 2 homologous regions from 6 different P 450 2 families were designed to capture a 440-bp cDNA fragment corresponding to the heme-binding region of P 450 2 isoenzymes. RT-PCR of EC total RNA with these primers amplified a 440-bp fragment. After gel purifn., the fragment was cloned, sequenced, and found to share a high degree of identity with **human liver** P 450 2C8 and 2C9. New primers were designed based on the nucleotide sequences of the 440-bp fragment and a third homologous upstream region from the 440-bp fragment. RT-PCR was used to capture 5' sequences upstream from the 440-bp fragment and lock-docking 3'-RACE was used to capture sequences downstream from the 440-bp fragment. These steps successfully expanded the no. of nucleotides captured and sequenced to 1.4 kb. The partial clone was a homologous to **human liver** P 450 2C8, sharing a >99.8% identity, and >86.1% with P 450 2C9. When sequence anal. of independently cloned 440-bp fragments was performed, no other P 450 2 isoenzymes were detected. To det. if P 450 2C isoenzyme family members were capable of AA epoxidn., ECV-304 cells, which usually generate low levels of EETs were transfected with pcDNA3 plasmids contg. DNA encoding functional P 450 2C9. Transient P 450 2C9 transfection of this eternal endothelial cell line increased EET prodn. levels up to 4-fold, which was similar in magnitude to EET prodn. by EC exposed to native low-d. lipoprotein (n-LDL). These data indicate that EC epoxidize AA by a P 450 2C8 isoenzyme.

L7 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 9
AN 1994:27992 CAPLUS
DN 120:27992
TI Identification of the fetal liver cytochrome CYP3A7 in human endometrium and placenta
AU Schuetz, John D.; Kauma, Scott; Guzelian, Philip S.

CS Med. Coll. Virginia, Dep. Med., Richmond, VA, 23298-0267, USA
SO Journal of Clinical Investigation (1993), 92(2), 1018-24
CODEN: JCINAO; ISSN: 0021-9738
DT Journal
LA English
AB Placenta and endometrium carry out steroidogenic biotransformation reactions such as 6-.beta.-hydroxylation of cortisol, a reaction characteristic of the dominant family of cytochromes P 450 in **human liver**, CYP3A. To investigate the possible role in these extrahepatic tissues of the CYP3A microsomal hemoproteins, the authors analyzed placental and endometrial microsomes on Western blots developed with an anti-human CYP3A antibody. The authors found an immunoreactive 51,500-D protein that migrated between CYP3A3 (HLp) and CYP3A5 (HLp2) identical with CYP3A7 (HFLa). CYP3A7, a form found prominently in human fetal liver microsomes, was first isolated as a liver 16-.alpha.-dehydroepiandrosterone sulfate hydroxylase. Northern blot anal. of total RNA isolated from placenta or from endometrium demonstrated a single band that cross-hybridized with a CYP3A7 cDNA. Amplification of the same RNA samples with the use of primers specific for CYP3A7 produced a 552-bp segment that had the predicted size and the same DNA sequence as does liver CYP3A7 cDNA. Hybridizable endometrial CYP3A7 mRNA was detected more frequently (six of seven samples) and in higher amts. (.apprx.12-fold higher) in pregnant compared with nonpregnant women (4 of 12 samples). In addn., during the secretory phase of the menstrual cycle CYP3A7 expression was sixfold higher than in the one sample from the proliferative phase that had detectable CYP3A7 mRNA. Moreover, the amts. of placental and endometrial CYP3A7 mRNA and protein increased substantially from the first to the second trimester of pregnancy. The authors conclude that placenta and endometrium **express** the same P **450** as is found in fetal liver. These tissues represent a previously unrecognized and quant. important site for 6-.beta.-hydroxylation and 16-.alpha.-hydroxylation of specific steroid precursors, possibly for protection of the fetus from the toxic effects of endogenous steroids and foreign substrates.

L7 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 10
AN 1992:253798 CAPLUS
DN 116:253798
TI Interleukin-6 down regulates the expression of transcripts encoding cytochrome P450 IA1, IA2 and IIIA3 in human hepatoma cells
AU Fukuda, Yoshiaki; Ishida, Nobuhiro; Noguchi, Teruhisa; Kappas, Attallah; Sassa, Shigeru
CS Rockefeller Univ., New York, NY, 10021, USA
SO Biochemical and Biophysical Research Communications (1992), 184(2), 960-5
CODEN: BBRCA9; ISSN: 0006-291X
DT Journal
LA English
AB Effects of human interleukin-6 (hIL-6), the major acute phase inducer, on the expression of transcripts encoding cytochrome P 450s were examd. in human hepatoma-derived cells. Using reverse-transcription polymerase chain reaction, it was demonstrated that 3 hepatoma cell lines, **HepG2**, HepG2f, and Hep3B, **express** P **450** mRNAs encoding IA1, IA2, and IIIA3, the major P 450 isoenzymes involved in carcinogen metab., and that they also show induction responses to treatment with their specific inducers. When hepatoma cells were treated with hIL-6, the levels of IA1, IA2, and IIIA3 mRNAs were markedly suppressed. Thus, down regulation of cytochrome P 450s may occur during the acute phase reaction, which may result in alterations in drug biotransformation.

L7 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2002 ACS
AN 1992:485812 CAPLUS
DN 117:85812
TI Optimization of yeast-expressed **human liver** cytochrome P450 3A4 catalytic activities by coexpressing NADPH-cytochrome P450

reductase and cytochrome b5
AU Peyronneau, Marie Anne; Renaud, Jean Paul; Truan, Gilles; Urban, Philippe; Pompon, Denis; Mansuy, Daniel
CS Cent. Natl. Rech. Sci., Univ. Paris, Paris, F-75270, Fr.
SO European Journal of Biochemistry (1992), 207(1), 109-16
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English
AB **Human liver** P 450 NF25 (CYP3A4) had been previously expressed in Saccharomyces cerevisiae using the inducible GAL10-CYC1 promoter and the phosphoglycerate kinase gene terminator (Renaud, J. P. et al., 1990). The use of an improved expression vector (Urban, P. et al., 1990) increased the amts. of P 450 NF25 produced/culture medium by a factor of five, yielding up to 10 nmol/L. The availability of recently developed host cells that simultaneously overexpress yeast NADPH-P **450** reductase and/or **express human liver** cytochrome b5, obtained through stable integration of the corresponding coding sequences into the yeast genome, led to biotechnol. systems with much higher activities of yeast-expressed P 450 NF25 and with much better ability to form P 450 NF25-iron-metabolite complexes. Nine-fold, 8-fold, and 30-fold rate increases were found resp. for nifedipine 1,4-oxidn., lidocaine N-deethylation and testosterone 6.beta.-hydroxylation between P 450 NF25-contg. yeast microsomes from the basic strain and from the strain that both overexpresses yeast NADPH-P 450 reductase and expressed human cytochrome b5. Even higher turnovers (15-fold, 20-fold and 50-fold rate increases) were obtained using P 450 NF25 contg. microsomes from the yeast just overexpressing yeast NADPH-P 450 reductase in the presence of externally added, purified rabbit liver cytochrome b5. This is explained by the fact that the latter strain contained the highest level of NADPH-P 450 reductase activity. It is noteworthy that for the three tested substrates, the presence of human or rabbit cytochrome b5 always showed a stimulating effect on the catalytic activities and this effect was saturable. Indeed, addn. of rabbit cytochrome b5 to microsomes from a strain expressing human cytochrome b5 did not further enhance the catalytic rates. The yeast expression system was also used to study the formation of a P 450-NF25 - iron-metabolite complex. A P 450 Fe(II)-(RNO) complex was obtained upon oxidn. of N-hydroxyamphetamine, catalyzed by P 450-NF25-contg. yeast microsomes. In microsomes from the basic strain expressing P 450 NF25, 10% of the starting P 450 NF25 was transformed into this metabolite complex, whereas more than 80% of the starting P 450 NF25 led to complex formation in microsomes from the strain overexpressing yeast NADPH-P 450 reductase. These results show that specific activities of yeast-expressed P 450 NF25 may be artificially low, owing to limiting amts. of the assocd. microsomal redox proteins and emphasize the importance of controlling the amts. of the different components of the monooxygenase complex in order to optimize these catalytic activities, esp. when the expression system is to be used for demonstrating metabolic capacities towards new substrates.

L7 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 11
AN 1991:508335 CAPLUS
DN 115:108335
TI A tobacco smoke-derived nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, is activated by multiple human cytochrome P 450s including the polymorphic human cytochrome P 4502D6
AU Crespi, Charles L.; Penman, Bruce W.; Gelboin, Harry V.; Gonzalez, Frank J.
CS GENTEST Corp., Woburn, MA, 01801, USA
SO Carcinogenesis (1991), 12(7), 1197-201
CODEN: CRNGDP; ISSN: 0143-3334
DT Journal
LA English
AB A human B-lymphoblastoid cell line, designated 2D6/Hol, which stably **expresses** human cytochrome P **450** CYP2D6 cDNA was

developed . This cell line exhibits bufuralol 1'-hydroxylase activity and immunol. detectable CYP2D6 protein. The specific activity of (+)-bufuralol 1'-hydroxylase in microsomes from 2D6/Hol cells was comparable to that obsd. in **human liver** microsomes. This cell line was used to examine the mutagenicity activation of 3 tobacco smoke-derived nitrosamines, N-nitrosonornicotine (NNN), 1-(N-methyl-N-nitrosamino)-1-(3-pyridinyl)-4-butanal) (NNA), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), by CYP2D6. Exposure of 2D6/Hol cells to NNK concns. of 30-90 .mu.g/mL induced a concn.-dependent decrease in relative survival and an increase in the mutant fraction at the hypoxanthine guanine phosphoribosyl transferase (hprt) locus. In contrast, NNK was non-mutagenic and non-cytotoxic to control cells at exposure concns. up to 150 .mu.g/mL. NNK mutagenicity in 2D6/Hol cells was compared to the responses obsd. in isogenic cell lines expressing human CYP1A2 (1A2/Hol), human CYT2A3 (2A3/Hol) and human CYP2E1 (2E1/Hol). These 3 addnl. human cytochrome P 450-expressing cell lines were also sensitive to NNK-induced mutagenicity and cytotoxicity. There was no evidence for CYP2D6-mediated activation of NNN or NNA. NNN was non-cytotoxic and non-mutagenic to both control and 2D6/Hol cells. NNA was equally cytotoxic and mutagenic to control cells and 2D6/Hol cells. The activation of NNA to a mutagen may have been carried out by P 450 native to the AHH-1 TK+/- cell line. The 2D6/Hol cell line, in conjunction with the control cell line and other isogenic cell lines expressing other human cytochrome P 450 cDNAs, provides a useful system for the examn. of the role of the polymorphic CYP2D6in human procarcinogen activation and drug metab.

L7 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 12
AN 1991:21329 CAPLUS
DN 114:21329
TI Immunohistochemical detection of cytochrome P450 isoenzymes in cultured human epidermal cells
AU Van Pelt, Frank N. A. M.; Meierink, Yvonne J. M. Olde; Blaauboer, Bas J.; Weterings, Peter J. J. M.
CS RCC NOTOX B. V., Hertogenbosch, 5231 DD, Neth.
SO Journal of Histochemistry and Cytochemistry (1990), 38(12), 1847-51
CODEN: JHCYAS; ISSN: 0022-1554
DT Journal
LA English
AB Specific monoclonal antibodies (MAb) to human cytochrome P 450 isoenzyme were used to det. the presence of these proteins in human epidermal cells. Two MAb (P 450-5 and P 450-8) recognize major forms of hepatic cytochrome P 450 involved in biotransformation of xenobiotics. A 3rd MAb, to cytochrome P 450-9, is not fully characterized. The proteins were detd. by the indirect immunoperoxidase technique after fixation with methanol and acetone. Biopsy materials for cultured keratinocytes, i.e., foreskin and hair follicles, contained the 2 major forms of cytochrome P 450. In cultured keratinocytes derived from hair follicles the proteins were undetectable, whereas the keratinocytes derived from foreskin continued to express the 2 major forms of hepatic cytochrome P 450. Cultured human fibroblasts and a human keratinocyte cell line (SVK14) showed staining similar to that of the foreskin keratinocytes. Cytochrome P 450-9 was detectable only in **human hepatocytes**. Apparently, under the culture conditions applied, cultured human foreskin cells and the cell line SVK14 continue to **express** specific cytochrome P **450** isoenzymes in culture, in contrast to hair follicle keratinocytes.

L7 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 13
AN 1990:434332 CAPLUS
DN 113:34332
TI Metabolism of fluperlapine by cytochrome P450-dependent and flavin-dependent monooxygenases in continuous cultures of rat and human cells

AU Fischer, V.; Wiebel, F. J.
CS Drug Saf. Dep., Sandoz Ltd., Basel, CH-4002, Switz.
SO Biochemical Pharmacology (1990), 39(8), 1327-33
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB The metab. of fluperlapine (I), a neuroleptic dibenzazepine deriv. with a N-methylpiperazinyl substituent, was investigated in continuous cultures of rat and human cells which **express** various cytochrome P **450**-dependent monooxygenase activities. The differentiated rat hepatoma cells H4IIEC3/G- and their variants 2sFou and FGC-5 metabolized fluperlapine predominantly by N-oxygenation and only to a minor degree by N-demethylation or glucuronidation of primary phenolic products. Total fluperlapine metab. in dedifferentiated rat hepatoma cells H5 and partially differentiated human hepatoma cells **HepG2** was much smaller than in the differentiated rat hepatoma lines. This was primarily attributable to their low capacity for N-oxygenation. Human long adenocarcinoma lines NCI-H322 and NCI-H358 formed only trace amts. of fluperlapine N-oxide. Pretreatment of 2sFou cells with benz(a)anthracene, phenobarbital or dexamethasone markedly increased the formation of N-demethylated and glucuronidated products but did not affect the rate of N-oxide formation. Guanethidine and cysteamine, inhibitors of flavin-dependent monooxygenase activity, reduced fluperlapine N-oxidn. more strongly than aldrin epoxidn., a marker for cytochrome P 450 activity. In contrast, n-octylamine inhibited aldrin epoxidn. but was without effect on fluperlapine N-oxygenation. The results suggest that certain cells in continuous culture are capable of expressing flavin-dependent monooxygenase(s) in addn. to cytochrome P 450-contg. monooxygenases. Such cells may offer useful systems for studying the oxidative metab. of a broad spectrum of xenobiotics and analyzing the importance of the two oxygenation reactions for the biol. effects of their substrates.

L7 ANSWER 18 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 14
AN 1990:424178 BIOSIS
DN BA90:84979
TI EXPRESSION OF CYTOCHROME P-450 ENZYMES IN CULTURED **HUMAN HEPATOCYTES**.
AU MOREL F; BEAUNE P H; RATANASAVANH D; FLINOIS J-P; YANG C S; GUENGERICH F P; GUILLOUZO A
CS UNITE DE RECHERCHES HEPATOL., INSERM U49, HOPITAL PONTCHAILLOU, F-35033 RENNES CEDEX, FR.
SO EUR J BIOCHEM, (1990) 191 (2), 437-444.
CODEN: EJBCAI. ISSN: 0014-2956.
FS BA; OLD
LA English
AB Hepatocytes from adult and newborn humans were put into primary culture and exposed to phenobarbital, 3-methylcholanthrene, or rifampicin, three well-known inducers of cytochrome P-450 in animals. The expression of four cytochrome P-450 enzymes (or groups of enzymes, namely P-450 IIIA, P-450 IIC8/9/10, P-450 IIE1, and P-450 IA2) was investigated. These enzymes were found to remain expressed during the period of culture studied. Treatment with the inducers for three days resulted in different responses, depending upon the inducer and the enzyme. Phenobarbital and rifampicin increased P-450 IIC8/9/10 mRNA transcripts and the corresponding protein, while 3-methylcholanthrene was ineffective. Both P-450 IIIA mRNA and protein were strongly induced by rifampicin. All of the hepatocytes were found to synthesize P-450 IIIA in response to rifampicin, as shown by immunoperoxidase staining. P-450 IIIA expression was not affected by phenobarbital and was decreased by 3-methylcholanthrene. P-450s IA2 and IIE1 decreased to 25-50% of the initial level during these cultures. P-450 IA2 and ethoxyresorufin O-deethylase activity (which is a monooxygenase activity related to P-45 IA family) were increased only by

3-methylcholanthrene and did not respond to the other inducers. P-450 IIE1 was not induced by any of these compounds. P-450 IIC8/9/10 and P-450 IIIA mRNA levels were also measured in **human hepatocytes** from one newborn. P-450 IIC8/9/10 was barely expressed in freshly isolated cells but increased dramatically with time in culture. P-450 IIIA transcripts were abundant in both freshly isolated and cultured cells derived from a newborn. These results clearly demonstrate that **human hepatocytes** continue to **express** cytochrome P-**450** enzymes and respond to inducers in culture. This model system provides a useful approach for investigating the effects of drugs on maturation and expression of drug-metabolizing enzymes in **human liver**.

L7 ANSWER 19 OF 19 FEDRIP COPYRIGHT 2002 NTIS
AN 2002:147484 FEDRIP
NR CRISP 1R01CA90214-01A1
TI MOLECULAR REGULATION OF LRAT AND CYP26 IN LIVER
SF Principal Investigator: ROSS, A. C; PENNSYLVANIA STATE UNIVERSITY, S-136C HENDERSON BLDG, UNIVERSITY PARK, PA 16802
CSP PENNSYLVANIA STATE UNIVERSITY-UNIV PARK, UNIVERSITY PARK, PENNSYLVANIA
CSS Supported By: NATIONAL CANCER INSTITUTE
FYR 2001
FU New Award (Type 1)
FS National Institutes of Health
SUM Retinoic acid and related retinoids are potent hormone-like ligand for two famil ies of ligand-activated nuclear receptors, RAR and RXR. Retinoic acid is synthes ized from vitamin A precursors in a variety of cells where it potentially acts i n situ to induce gene expression, control growth, and promote normal cellular di fferentness. These actions make retinoids a great interest in situ chemopreventi on of cancer. Despite many advances in retinoid receptor biology, our understand ing of the factors that regulate endogenous retinoid concentrations has lagged b ehind. Understanding the production and catabolism of retinoids is critical to u nderstanding their receptor-mediated actions. The central hypothesis to be teste d is that two liver microsomal enzymes - lecithin: retinol acyltransferase, LRAT , and cytochrome P450RA1, or CYP26- serve as key regulators of Retinoic acid bio synthesis and catabolism, respectively. Recently we have cloned LRAT cDNA from r at and mouse liver. Preliminary studies are presented in which LRAT and CYP26 ge ne expression was strongly regulated in liver, both actually by exogenous retino ids and chronically by dietary vitamin A. To critically test our hypothesis we w ill conduct 4 specific aims. In aim 1 we will examine retinoid- and diet-induce d differences in LRAT and CYP26 gene expression and retinoid metabolism in intac t rats. In aim 2 we will investigate which liver cell types **express** LRAT and **CYP** 26 and further test our model of retinoid metabolism in hepatocytes and stellate cells. In aim 3, we will sequence the homolo gous cDNA for **human liver** LRAT and conduct molecular studies of LRAT and CYP26 expression in normal and diseased li ver specimens available from the Liver Tissue Procurement and Distribution Syste m (LTPADS). In aim 4, we will study the 5' regulatory regions of the LRAT and CY P26 genes to determine the molecular basis for their responsiveness to Retinoic acid in liver. By investigating both LRAT and CYP26 simultaneously we expect to obtain novel insights into the molecular and cell-type specific regulation of Re tinoic acid biosynthesis and degradation. This information could shed new light on the endogenous factors that control the availability of Retinoic acid in tiss ues and plasma which, in turn, are likely to affect Retinoic acid's anticarcinog enic potential.

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